Vol. 67, No. 8 Established 1884 August 1950

ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

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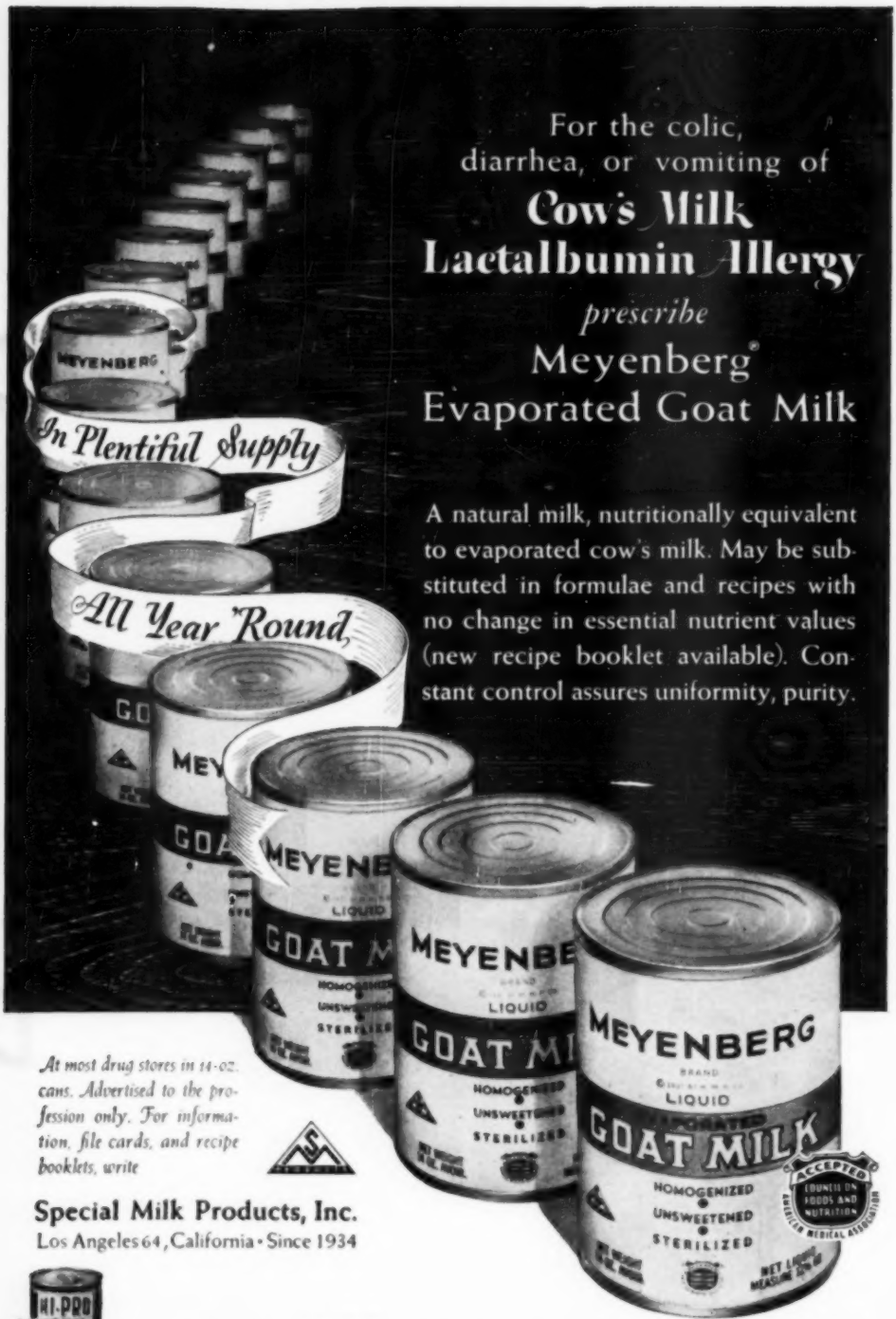

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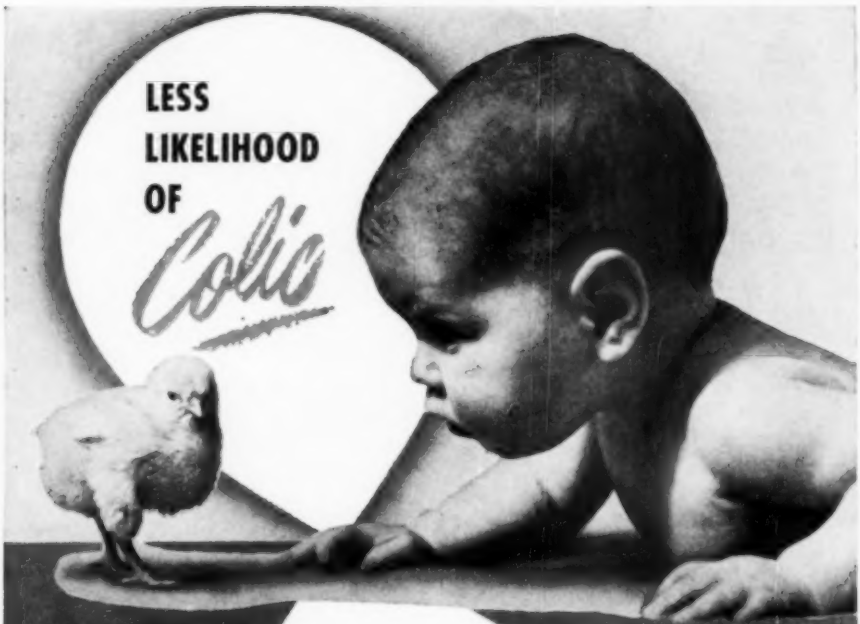

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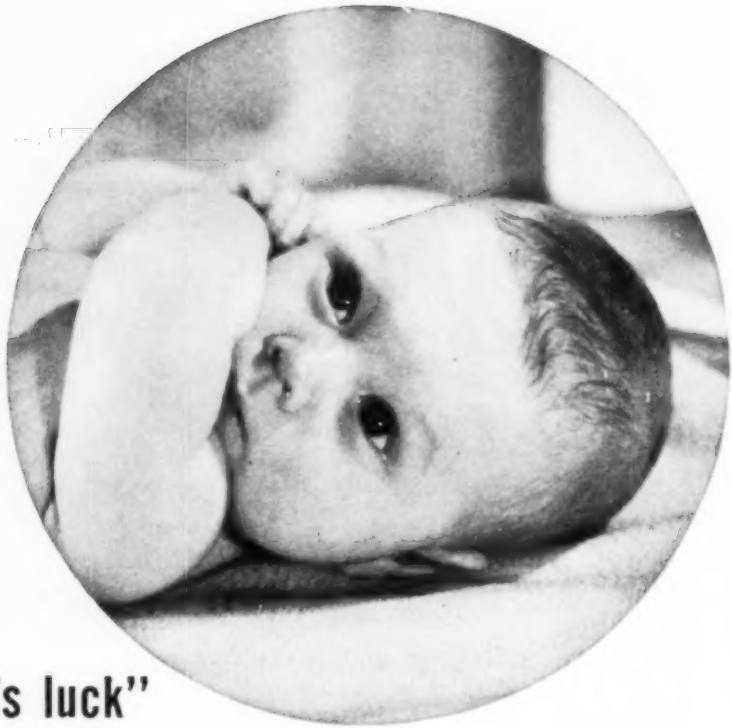

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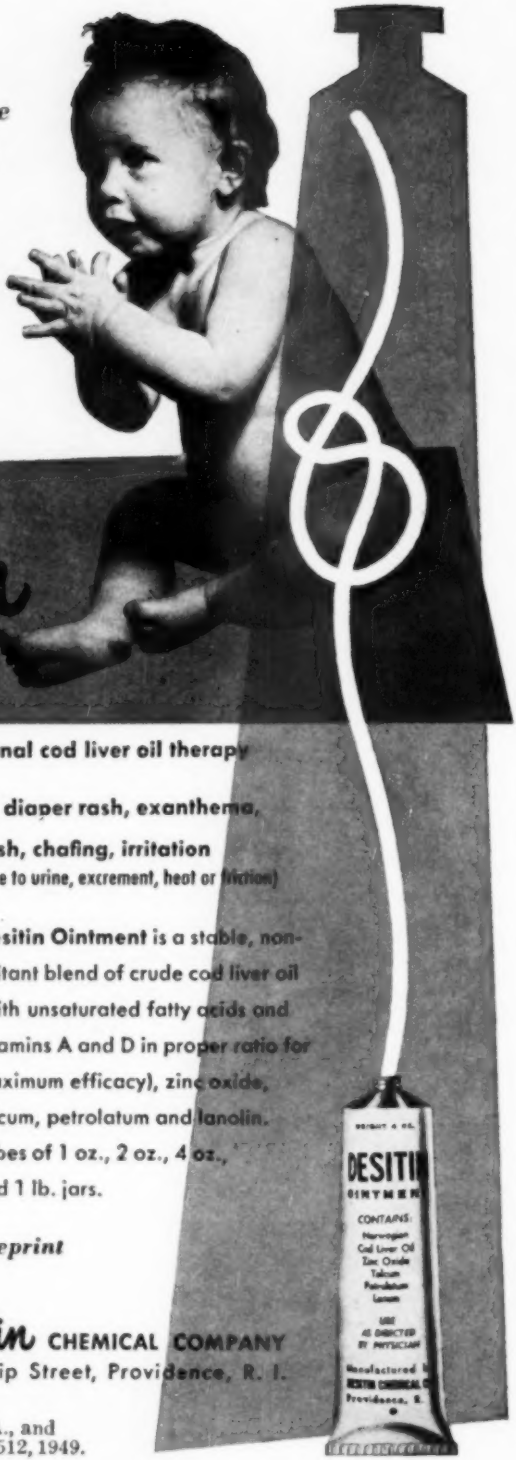

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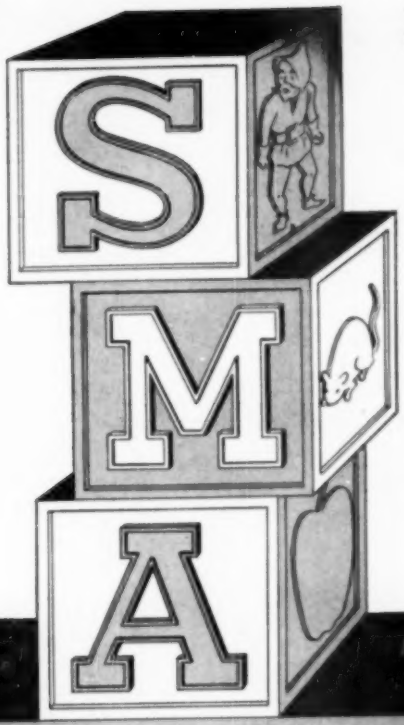

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ACUTE ALIMENTARY TOXICOSIS*

A. SHAFIK ABBASY, M.B., D.CH., M.D.
AND
M. MAMDOUH HANAFY, M.B., D.CH., M.D.
Alexandria, Egypt.

Late in the 19th century, acute intestinal toxicosis was first described as a condition secondary to diarrhea. It was prominently characterized by severe constitutional symptoms similar to those which accompany poisoning. The disease still occurs almost exclusively in infants and young children, whose great susceptibility to the acute forms of intestinal toxemia is probably due to a number of causes, the most important of which is the great irritability and immaturity of their nervous system. Such instability makes it possible for slight disturbing factors, e.g., toxins absorbed from the intestinal canal, to produce maximal effects such as high fever, pronounced drowsiness, cerebral vomiting, convulsions, coma, and even death.

The most alarming manifestations of acute alimentary toxemia may be divided into two outstanding syndromes[1]:

1. Peripheral circulatory failure.
2. Acute encephalopathy.

Variable combinations of these two may be encountered and each may be recognized in pure form. Sometimes neurologic manifestations occur very early in the illness and may precede the onset of diarrhea and/or vomiting.

*From the Pediatric Department and Children's Hospital, Faculty of Medicine, Farouk I University, Alexandria, Egypt.

While our knowledge as regards the actual offending agent or agents which produce acute intestinal toxemia is very unsatisfactory and has not shown any appreciable advance during the last fifty years, yet there is no doubt that such a toxemia exists and that it is one of the most important factors in producing nervous symptoms.

A number of theories have been suggested to explain the relationship between diarrhea and toxicosis, the most important of which are:

(1) Those related to water and electrolyte balance, especially sodium and potassium ions in the body[4]; but it was found that shock often persists after the electrolyte and fluid loss has been corrected and death follows in many cases in spite of the correction.

(2) Toxins either produced by the organisms or formed in the body from food and/or secretions. Bacteriological study showed no stability in the type of organism present.

(3) Dysentry organisms, especially Shiga infection, may be the cause. The organism presumably does not grow diffusely throughout the contents of the enteric tract, but rather on or in the wall of the bowel[3]. Bacteriological study of stools and blood gave uneven results both as regards the positivity of cultures and the type of organism isolated.

(4) Virus infection, especially in the newly born, may cause epidemic enteritis but toxicosis is not a part of their clinical picture.

In cases of acute alimentary toxemia, virus studies on clinical-pathological and inoculation bases gave negative results[5].

Thus none of these hypotheses can alone explain the cause of toxemia. More than one of them may act in conjunction to produce it. The whole problem needs further and detailed investigations to establish its etiology.

Our present work is concerned with the clinical and therapeutic aspects of the disease and the results obtained by the different chemotherapeutic and antibiotic agents. In a previous paper of one of us (Abbasy[2]), the results of using sulfaguanidine and sulfapyridine were recorded. With the first drug there was no reduction in the mortality rate as compared with controls treated symptomatically only. By using sulfapyridine the fatality rate was reduced from 62.5 to 37.5 per cent and to 7.5 per cent only if the

cases who died within the first 24 hours of admission were excluded. Later on* with the aim to obtain rapid and high sulfonamide blood levels, soluble sulfadiazine was given intrasmuscularly immediately on admission and then oral administration begun and continued. This scheme did not reduce the mortality any further. When penicillin became available he tried it also; contrary to Meyers[7] results with this antibiotic failed completely.

In this work other absorbable sulfonamides were tried as well as parenteral and oral streptomycin and comparative study of the results was given.

Cases were admitted to the children hospital and represented members of the general population of the poor class. The work covered two complete years (1948 and 1949). The total number of collected cases amounted to 105. The drugs used were sulfathiazol, sulfadiazine, streptomycin parenterally and by mouth, and a combination of oral streptomycin and sulfadiazine. There was no selection of a certain drug to a particular case. On the contrary, there was a trial of giving the above mentioned five groups of drugs to five collections of cases showing relative similarity in clinical manifestations. Sulfathiazol in doses of 0.15 gm. per kg. per day divided in 4 hourly doses was given to 30 cases. Sulfadiazine, in the same amounts and intervals was given to 20 cases. Half a gram of streptomycin divided in three equal parts was administered intramuscularly every 8 hours to 26 patients. Oral streptomycin in doses of ¼ gm. every 6 hours was given to 18 cases, while 11 cases received this amount of the antibiotic orally together with sulfadiazine in the previously mentioned quantities.

Additional lines of treatment included repeated administration of saline and/or glucose and circulatory stimulants. Initial starvation followed by high protein, low fat and moderate carbohydrate diet suitable for every age group was given.

ANALYSIS OF CASES AND FATALITY RATES

Season. 76 per cent of the cases occurred during May, June and July; 88.5 per cent of the cases occurred in the six months starting with April, while the remaining 11.5 per cent occurred during the other half of the year.

*Unpublished work of S. Abbasy.

Age

Age in Months	Incidence Rate	Fatality Rate
1- 6	36.2%	16 %
6-12	55.2%	12 %
12-30	8.6%	33 %
1-30	100 %	16.2%

Sex. 61 per cent of the cases were males while 39 per cent were females. The mortality rate among both groups was almost equal.

Method of Feeding

Method of Feeding	Incidence Rate	Fatality Rate
Breast	25%	20 %
Artificial	20%	10 %
Mixed	55%	16.4%

Previous State of Nutrition

Degree of Loss of Wt. Compared with the Expected Wt. for Age in Egyptians	Incidence Rate	Fatality Rate
Normal Wt. to 15% below	20 %	4.8%
15% to 30% "	40 %	9.5%
30% to 50% "	32.4%	17.6%
More than 50% "	7.6%	75 %

Onset of Gastro-Intestinal Manifestations Before Admission

Days	Incidence Rate	Fatality Rate
1- 7	70.5%	10 %
7-14	20 %	14.3%
More than 14	9.5%	70 %

Onset of Nervous Manifestations

Type of Onset	Incidence Rate	Fatality Rate
Sudden	76%	11%
Gradual	24%	32%

Degree of Nervous Affection

Degree	Incidence Rate	Fatality Rate
Mild	22.9%	8.3%
Moderate	44.7%	17 %
Severe	32.4%	20.6%

Dehydration

Degree	Incidence Rate	Fatality Rate
Absent	20%	10 %
Moderate	62%	9.7%
Marked	18%	47 %

Shock. Peripheral circulatory failure was a very bad sign. When very marked the patient either died on or shortly after admission to hospital, but when it was of less severity the prognosis was brighter.

Vomiting was a prominent symptom. It was moderate in 25 per cent of cases, marked in 55 per cent and excessive in 20 per cent. However severe, it did not interfere with the administration of drugs and it rapidly ceased.

Diarrhea. It was mild and started after the start of toxic symptoms in 20 per cent of cases. In the rest of the patients it was either moderate or severe.

Pyrexia. Normal and subnormal temperature has been met with in 18 patients, 12 of them died. In the rest of cases the temperature ranged between 38° and 40° C. and occasionally more. In two-thirds of the cases the temperature subsided within two or three days of treatment. While in the rest one or more days were necessary for the temperature to fall down.

Results

Group	Drug Used	Number of Cases Treated	Fatality Rate
I	Sulfathiazol	30	17 %
II	Sulfadiazine	20	20 %
III	Streptomycin I.M.	26	23 %
IV	Streptomycin orally	18	11 %
V	Streptomycin orally + sulfadiazine	11	0
	Totals	105	16.2%

COMMENT

Compared with the very high incidence of cases of infantile diarrhea, acute alimentary toxicosis is fortunately an uncommon syndrome. It has its maximum incidence during the hot months of the year, affecting infants and young children of both sexes. It is more frequent at the beginning of mixed feeding. The fatality rate is very high among the poorly nourished, and in patients with previously neglected gastro-intestinal derangements. It seems that the severity of encephalopathy does not affect so much the fatality rate while severe peripheral circulatory failure and dehydration are often fatal.

Sulfathiazol and sulfadiazine gave nearly similar results, the fatality rates being 17 and 20 per cent, respectively, as compared with 37.5 per cent when using sulfapyridine. These good results are comparable with those reported by one of us (Hanafy[6]) in cases of gastro-enteritis. Streptomycin when given parenterally was not as effective as the chemotherapeutic drugs, but when given orally the results were strikingly good, having reduced the fatality rate to 11 per cent only. The group which received both chemotherapy and oral streptomycin proved to be the best, although the number of cases were not many. We think that this is the method of choice up till now. With the recent availability of chloromycetin and aureomycin, their trial has been started, and the results will be reported in a future paper.

SUMMARY

1. A series of 105 strictly selected cases of acute alimentary toxicosis was divided into five groups.

2. Group I and II were given sulfathiazol and sulfadiazine, respectively. Group III was given streptomycin parenterally while Group IV was given this antibiotic by mouth. Group V received both streptomycin and sulfadiazine orally.

3. The case fatality rate in the whole series was 16.2 per cent.

4. Oral streptomycin proved to be a real advance in the treatment of the illness having reduced the fatality rate to 11 per cent. When combined with chemotherapy there were no deaths in the eleven treated cases.

5. Fatality rate was higher in cases starting mixed diet and in

those coming late or having recurrent or prolonged gastro-intestinal derangement prior to the onset of toxicosis.

6. Cases with severe wasting, marked dehydration, shock or pronounced manifestations have a narrow chance of survival.

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INHERITANCE OF FACTOR CAUSING SUDDEN DEATH. (Edinburgh Medical Journal, 57: 1, Jan. 1950). Leys cites a farmer's family in the Scottish Highlands showing dominant inheritance of a lethor or sublethal factor, with sudden death in adolescence or early adult life as the first symptom. Five of 8 children in one sibship died suddenly at the ages of 11, 13, 16, 16 and 23 years. A sixth suffered from syncopal attacks and died unexpectedly when under treatment for pulmonary tuberculosis. The surviving siblings showed some evidence of cardiac conduction defect and a tendency to hypercholesteremia. Xanthomatous patches of the planus type were observed on the skin of some of the siblings. Coronary atheroma was not a feature of the syndrome. The available evidence points to a conduction defect being probably associated with the cause of death, while not necessarily the cause of death, and to exertion as a preceding rather than a coincidental factor. The absence of evidence of coronary disease was striking. The pathological alterations in the heart muscle of one member of the family who died suddenly were absence of foam cells and of glycogen and presence of a perivascular fibrosis. The importance of the minor degrees of conduction defect is difficult to assess, but it appears that persons who carry the factor and escape death in early life tend to have gross cardiac conduction defects in early middle life. It is significant that all the persons examined had slow heart rates. The detection of hypercholesteremia or of xanthomatous patches of planus type in the skin in more than one sibling is suggestive of an inherited metabolic disorder.—*Journal A.M.A.*

SINUSITIS AND THE PRERHEUMATIC CHILD

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The child with sinusitis and the prerheumatic child show an exact correspondence of symptoms, a relationship hitherto unreported. The significance of this observation lies in the possibility that infection in the sinuses may be responsible for subsequent rheumatic phenomena.

Careful observers, describing respectively the "prerheumatic child," and the "child with sinusitis," report many symptoms which, when compared, are identical.

Prerheumatic Symptoms. Coburn[1] mentions the symptoms found in the prerheumatic child as "anorexia, failure to gain weight, apathy, pallor, nausea, mild elevation of body temperature, aches, fatigue, anemia, twinges of precordial pain, headaches, nervousness, bed-wetting, night terrors and many other phenomena." Coburn refers to the observations of Vining[2] who previously "emphasized the importance of these symptoms in the 'prerheumatic child.'"

Struthers[3] describes prerheumatic symptoms as pallor, underweight, anorexia, fatigue, aches and pains, sometimes associated with low grade fever and anemia, and frequent upper respiratory tract infections.

Elghammer[4] gives the following prerheumatic symptoms: fatigue, irritability, anorexia, pallor, night sweats, spontaneous epistaxis, increased pulse rate, low grade fever and vague pains in extremities, joints and abdomen.

Morgan[5] lists the following symptoms: tendency to become easily fatigued, bouts of unexplained fever, listlessness, restlessness, particularly in sleep, and failure to gain weight.

Symptoms of Chronic Sinusitis. Reisman,[6] discussing sinusitis, states: "The following is a tabulation of conglomerate symptoms of all children under observation in the Pediatric Clinic* and private practice in order of their frequency: cough, postnasal drip, fever, fatigue, tenderness over the antrum, poor appetite, retropharyngeal adenitis, nausea, vomiting, nasal discharge, asthma,

*Dr. Reisman preceded the author as Chief of the Pediatric Chest Clinic at the New York Post-Graduate Medical School and Hospital.

frequent colds, mouth breathing, expectoration, dark circles beneath eyes, headache, dizzy spells, sweats, hoarseness, pharyngitis, otitis media, mastoiditis, abdominal pain, underweight, cervical and submaxillary adenitis, hemoptysis and epistaxis, night terrors, rheumatic pain and frequent attacks of pneumonia."

Symptoms Common to the Prerheumatic Child and the Child with Sinusitis. Eight symptoms mentioned by Coburn as prerheumatic are identical with those noted by Reisman in sinusitis, namely anorexia, failure to gain weight, nausea, mild fever, aches, fatigue, headaches and night terrors.

Ten other symptoms in the prerheumatic child recorded by Coburn, Struthers, Elghammer and Morgan are also symptoms of sinusitis. Each is discussed briefly.

Apathy in the prerheumatic child may result from an aprosexia or inability to concentrate, a common symptom of sinusitis,[7,8] particularly upon arising. Lewis[9] noted among 100 consecutive cases of sinusitis that 90 per cent showed aprosexia.

Pallor occurs in active sinusitis. Pallor may accompany the *anemia* frequently present in both diseases or it may be due to peripheral vasoconstriction in a child with vasomotor instability.[1] In one child, treated for sinusitis for years at the New York Post-Graduate Hospital, the pallor was often so ghastly that the mother was repeatedly stopped on the street and advised to take the child to a doctor. Many blood counts in this child revealed a mild anemia, entirely out of proportion to the pallor.

Twinges of Precordial Pain were noted in several children treated for chronic sinusitis in the Chest Clinic at the New York Post-Graduate Hospital. *Abdominal pain*, commonly noted in sinusitis, is a frequent complaint in prerheumatic[4] and rheumatic children. In rheumatic children, all of whom had a complicating sinusitis,[10] precordial pain was noted particularly when the sinusitis was troublesome.

Nervousness, noted in the prerheumatic child, is a common symptom of chronic sinusitis. Lemere[11] observed "extreme nervousness" in children with sinusitis; Dunn and Dunn[8] reported "athetoid conditions," in reality subchoreic twitchings so common in children with active sinusitis.[12]

Bed-wetting, or enuresis, is often found accompanying sinusitis, and is worse during an exacerbation, or "cold."[13]

Frequent Upper Respiratory Tract Infections, mentioned as a prerheumatic symptom by Struthers, is noted by Reisman and many others as a sign of chronic sinusitis.[7, 14, 15, 16] Indeed, it is pathognomonic of chronic sinusitis.[17] Crooks and Signy[7] found frequent colds present in 83 per cent of 100 children with sinusitis.

Epistaxis, mentioned by Elghammer in the prerheumatic child, is a common symptom in active sinusitis. Streptococcal toxin in purulent exudates from sinusitis readily injures nasal mucous membrane.

Restlessness, particularly in sleep, noted by Morgan, is a characteristic symptom of chronic sinusitis, accounting for night terrors. Watson-Williams[18] finds that sinusitis may cause insomnia and nightmares. He states: "I have known patients who always find exacerbations of a sinusitis ushered in by a terrifying nightmare."

DISCUSSION

Vining[2] states that many of the symptoms in the prerheumatic child are no different than the symptoms found in large numbers of children attending the out-patient department. After working in a pediatric clinic for fourteen years, I can confirm this conclusion. These symptoms, as Vining points out, are present in toxic children. What is the source of this toxin?

All possible foci of infection must be ruled out as a cause of the symptoms already discussed. Infected tonsils and teeth can be discounted. Among our rheumatic children, 86 per cent had been tonsillectomized; yet symptoms continued. Their teeth had been placed in good repair. Only one focus was invariably present, an incurable chronic sinusitis.[10]

The swallowing of pus in children with chronic sinusitis destroys the appetite, produces nausea, particularly upon arising, and results in failure to gain weight. Headaches may be noted upon prolonged recumbency,[19] when pus accumulates in the sinuses. Toxins under tension in the sinuses enter the cervical nodes, invade the blood stream and produce fever, aches, twinges of precordial pain and nervousness.

Recognition that active chronic sinusitis causes prerheumatic and rheumatic symptoms may afford a prophylactic approach to the problem of rheumatic fever.

CONCLUSIONS

1. Eighteen symptoms in the prerheumatic child are identical with the symptoms noted in chronic sinusitis.

2. The prerheumatic child is the child with active chronic sinusitis.

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CHLORAMPHENICOL IN WHOOPING COUGH. (Lancet, London, 1: 400, March 4, 1950). Macrae treated 5 severely ill infants with a poor prognosis but at a relatively early stage of whooping cough, before secondary infections had developed. There was no clinical doubt of the diagnosis. The minimum daily dose was 50 mg. per kilogram of body weight. Each baby received 0.25 Gm. as a first dose and 0.125 Gm. every six hours thereafter for seven days and then 0.125 Gm. every 12 hours for seven days. There was an immediate improvement in general condition in all the cases, followed by rapid recovery.—*Journal A.M.A.*

ACUTE BROMIDE INTOXICATION*

Report of a Case in a Two-Year-Old Child

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and

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Bromide intoxication is unusual in children since bromides are seldom precribed today in pediatric practice. The condition in adults usually follows prolonged therapeutic use or self-medication.

Harris reported two cases in young children who had been taking bromides for several months. The symptoms were personality changes, hallucinations, restlessness and ataxia.

The case here reported is one of acute intoxication in a child following accidental ingestion of a single large dose of bromide.

CASE REPORT

S. G., a two-year-old female, was admitted to the pediatric service of Freedmen's Hospital on April 12, 1945, with a history of drowsiness and inability to stand since the previous day. On the day before admission she was seen with a bottle of sedative tablets prescribed for an adult member of the family. It was estimated that she ingested approximately 5 Gm. of sodium bromide and 120 mg. of phenobarbital. A few hours later she exhibited excessive thirst and a stumbling gait. The following day she was extremely drowsy and unable to stand without falling. Her speech was thick and incoherent.

On admission the child showed weakness, lethargy and ataxia. The pupils reacted sluggishly to light. Tendon reflexes were diminished. A fine papular rash was present on the face and in a few days had spread to involve the trunk and extremities. The temperature was normal. Her weight was 31 pounds ¾ ounces.

A moderate polymorphonuclear leukocytosis was present on admission but disappeared before discharge. The urine and spinal fluid were normal except for the presence of bromides. On admission the serum bromide level was within the toxic range. The blood Kahn reaction and the tuberculin skin test were negative.

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TABLE I. *Bromide and Chloride Concentrations in Body Fluids*

Date	Bromide (Serum) m.Eq./liter	Chloride as Cl (Plasma) m.Eq./liter	Bromide (Spinal Fluid) m.Eq./liter	Bromide (Gastric Juice) m.Eq./liter	Bromide Urine Qualitative
4-12-45.....	22	.....	.....	.....	Positive
4-13-45.....	.....	96	.....	.....	Positive
4-14-45.....	16	.....	.....	.....	.....
4-18-45.....	6	.....	9	.....	Negative
4-27-45.....	less than 3	107	.....	.....	.....
5- 2-45.....	.....	110	less than 3	.....	.....
5- 6-45.....	.....	115	.....	.....	.....
5- 8-45.....	.....	.....	.....	Less than 3	.....

Hypodermoclyses of 2½ per cent glucose in normal saline were given on the first two days. Sodium chloride (0.6 Gm. three times daily) was given by mouth for seven days.

Three days after admission she was still lethargic, but could stand without support. On the fifth day she was up and about the ward showing no symptoms except the rash which persisted about twenty days.

DISCUSSION

Bromides produce their sedative effect by direct depression of the central nervous system, particularly the higher cortical centers. Effects are cumulative since excretion is slow and since bromides tend to replace chlorides in the tissues and body fluids with the preferential excretion of chlorides by the kidney. Bromides diffuse readily into all the body fluids, including the gastric juice and spinal fluid. Serum levels over 18 m.Eq. per liter are considered toxic, but symptoms have been reported with lower levels, indicating variations in individual susceptibility. Plasma chlorides are not reduced after a single dose of bromide but may be when administration is continued for two weeks or more.

Two types of toxic reaction have been described: (1) simple depression with lethargy, confusion, weakness and ataxia, and (2) psychosis with delirium and hallucinations. Simple depression may follow either prolonged administration or a single large dose. Psychotic manifestations may begin after a few weeks to many months of medication.

The condition may not be suspected in chronic cases because the onset is insidious and the symptoms may appear to be exacerbations of pre-existing psychotic or neurotic disorders for which the medication was prescribed. Because of the confusion and ataxia, brain tumors, neurologic degenerative diseases, syphilis of the central nervous system and postencephalitic states may be considered in the differential diagnosis.

The suspicion of drug intoxication will usually be entertained in the acute cases because of the sudden onset of somnolence in a patient who shows neither acidosis nor evidence of infection. In all cases of acute drug intoxication, characterized by extreme somnolence or coma, blood bromide determinations should be made.

Treatment consists in the administration of sodium chloride and the forcing of fluids in order to hasten bromide excretion. Sodium chloride can usually be given by mouth and should be continued until symptoms disappear. Improvement should be prompt in acute cases since there has not been time for chloride displacement. In chronic cases, where chloride depletion is marked, bromide may be detectable in the urine for a few weeks and it may require one to three months for all symptoms to disappear.

SUMMARY

We have presented a case of acute bromide intoxication with prompt recovery in a two-year-old child following accidental ingestion of sedative tablets. The principal symptoms were weakness, lethargy and a generalized papular eruption. The differential diagnosis and treatment of acute and chronic bromism are discussed.

The clinical symptomatology of bromide intoxication was complicated by the presence of phenobarbital in the sedative ingested by the child.

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A CASE OF OVERDOSAGE OF PROPYLTHIOURACIL

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Recently Futcher and Massie[1] reported a case of agranulocytosis which developed in an adult patient after taking propylthiouracil for fifty-eight days. The total amount of the drug taken during this period of time could not have been more than 15,000 milligrams.

We should like to report a case in which 19,000 milligrams of propylthiouracil was taken by a young man in twenty days and no unusual change in the blood resulted. We have not been able to find in the medical literature any report of a large amount of this drug having been taken over a short period of time.

CASE REPORT

Male. Age 18 years. June 15, 1948.

Appendix has been removed. He has been weak and nervous and feels he has had a fever for the past year. Complains of being nauseated and considerable gas in the stomach during past month. Some headaches. Can feel his heart running fast and beating strong. Hands tremble. Urinates on an average of three times a night during the past two months. Appetite varies considerably, but it is very good most of the time. Weight loss twelve pounds during this time. He has done no work during the past six months.

Examination. Blood pressure: Systolic 150, diastolic 70. Weight: 152 pounds. Thyroid, both lobes are enlarged, soft throughout and no adenomas present. A bruit can be heard over both thyroid lobes. Fine tremor of the fingers. A systolic murmur can be heard over the whole heart area, rate is increased and sinus rhythm is present. Superficial reflexes are exaggerated. Basal metabolic rate plus thirty-six. Urine normal in every respect.

Blood: Leukocytes 11,650; polymorphonuclears 73 per cent (segmented 68, juvenile 5); lymphocytes 24 per cent; monocytes 3 per cent; red cells 5,112,000; red cells normal in size, shape and

color; hemoglobin 98 per cent. Sedimentation rate 14 millimeters in one hour (100 millimeter tube).

Diagnosis. Diffuse goiter with hyperthyroidism (Graves' disease).

Treatment. He was given a prescription for propylthiouracil tablets of 50 milligrams. Two (100 milligrams) were to be taken every eight hours (300 milligrams daily). In ten days his blood pressure was systolic 110, diastolic 70, heart was slow, rhythm normal and no more murmurs heard but he was nauseated. Blood and urine normal. He was seen twice a week. All was normal but the nausea increased. On the twentieth day the nausea was excessive and he was weak, but the blood and urine were normal. So he was quizzed carefully and it was found he had taken two tablets every two hours (12 times daily or 1,200 milligrams) for ten days and then 700 milligrams each day for ten more days, a total of 19,000 milligrams in twenty days. The drug was stopped and the nausea continued for eight days longer.

The lowest blood findings at any time were: leukocytes 5,250, granulocytes 62 per cent and hemoglobin 98 per cent. Urine normal.

On the twenty-eighth day he was started on the original dose of propylthiouracil and at the end of four months it was gradually reduced until at the end of eight months it was stopped entirely.

At no time during this period did he appear to be injured in any way and, with the exception of being nauseated and weak, he had no other reactions. His greatest weight during the time of treatment was 156 pounds.

Up to the time we saw this young man we had given the propylthiouracil tablets to each patient and no prescriptions had been written. A drug firm* had furnished us with propylthiouracil for experimental purposes for a period of about two years. At this time we had no propylthiouracil in the office so gave him our first prescription—two tablets (100 milligrams) every eight hours. The bottle was labeled two tablets each two hours.

Now, in June 1950, the patient reports no abnormal symptoms that could be traced to the propylthiouracil. A few months ago he was examined at the Mayo Clinic and told he had no symptoms of hyperthyroidism and that his blood was normal.

*Drug furnished by Eli Lilly and Company, Indianapolis, Indiana.

We have been lead to believe propylthiouracil is a dangerous drug. This is not our experience and especially since we have seen this young patient we have little fear of it.

SUMMARY

A patient, 18 years of age, took 19,000 milligrams of propylthiouracil in twenty days and at no time did he show any abnormal blood changes and the only symptoms which could be traced to the administration of the propylthiouracil were nausea and weakness.

His blood was entirely normal during a period of eight months following this and was reported normal within the last few months.

The amount of the drug taken in twenty days is equal to that ordinarily given in sixty-three days.

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PLASMA TRANSFUSIONS IN HEMOPHILIA. (Nederlandsch Tijdschrift v. Geneeskunde, Amsterdam, 93: 3714, Oct. 29, 1949). In an earlier communication van Creveld and Paulssen had observed that in hemophilia plasma prepared with heparin was more effective than that prepared with citrate. The transfusion of plasma to which a small quantity of heparin has been added as an anticoagulant reduces considerably the coagulation time of hemophilic patients. Products of the hydrolysis of heparin shortly after transfusion appear partly responsible for this shortening of the coagulation time. There seems to be a difference between the coagulation-promoting factor in citrated and heparinized plasma in favor of that in heparinized plasma. The characteristics of prothrombin also seem to differ in these two types of plasma. It is known that in the coagulation of hemophilic blood only a part of the prothrombin is used up. The authors investigated the prothrombin consumption in hemophilic patients before and after transfusions of citrated or heparinized plasmas and found that the consumption is only slightly or not increased after the transfusion of citrated blood, but after the transfusion of heparinized plasma much more of the prothrombin is used up.—*Journal A.M.A.*

CLINICAL REVIEW

In order to encourage the writing of clinical articles by recent graduates or senior medical students, the ARCHIVES *will publish monthly at least one such paper from the classes of Doctor Reuel A. Benson, New York Medical College, New York, and Doctor Philip Moen Stimson, Cornell Medical School, New York. Other interested medical schools are cordially invited to submit student papers for consideration.*

RELATION OF RUBELLA IN PREGNANCY TO CONGENITAL DEFECTS*

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Since the original observations of Gregg,[1] in 1941, over 200 cases of congenital defects in which there was maternal rubella during the first trimester have been recorded. It is the purpose of this paper to critically review the existing literature to determine the frequency of defects and what measures may prove of value in prophylaxis.

The occurrence of an unusual type of cataract was noted in children in Australia in 1941. "The remarkable similarity of the opacities in the lens, frequency of an accompanying affection of the heart, and the widespread geographic incidence of the cases suggested that there was some common factor.....the result of some constitutional disturbance of toxic or infective nature rather than of a purely developmental defect."[2] The possibility of an infection in pregnancy was considered and in calculating backwards from the birth of these children, it was observed that there had been a severe epidemic of rubella in 1940. The time of this epidemic corresponded with the first trimester of pregnancy of the mothers of these children. By means of questionnaires a total of 78 cases were studied. In addition to the cataracts which were usually bilateral, other eye defects noted, but not in every case, were microphthalmia and a coarse nystagmus. In addition, there were numerous instances of malnourishment, cardiac defects and mental retardation.

A committee was organized to determine the following: (a) Was the disease rubella? (b) In what period of pregnancy did

*Submitted as partial fulfillment of the requirements of the course in Senior Pediatrics at the New York Medical College, Flower and Fifth Avenue Hospitals.

most of the defects occur? (c) What is the full range of defects? (d) What other infectious diseases cause similar defects?

A second report of the committee added eight more cases of defects of which seven had a history of maternal rubella. Swan believed that clinically the disease was rubella but admitted that actual proof could be obtained only by isolating the virus at the time of the attack in the mother.

In 1946,[3] the Australian group added 58 additional cases of congenital defects to the series. In 42 cases, the maternal disease was rubella of which 37 cases occurred in the first trimester. In two cases, rubella was believed to have occurred two weeks prior to conception.

There were 27 cases of deaf-mutism and speech defects, four ocular defects and 19 cardiac defects (and 5 additional "doubtfuls").

Stockard's experimental work on the minnow is noted here and his conclusions summarized: (a) The type of abnormality is determined by the time at which the factor operates in relation to development. (b) The earlier the factor operates, the greater the defect. (c) If at a time of no rapid change—no injury. This fitted in with clinical observation.

In this country, the first report was by Reese,[4] who added 3 cases, all of whom had cardiac defects and in addition 2 showed bilateral cataracts. Rubella had been diagnosed (?) in all 3 mothers in the first month of pregnancy. Perera[5] added an additional case of right congenital cataract, feeding difficulties and patent ductus in a child whose mother had rubella in the second month of pregnancy.

Other investigators added rapidly to the growing number of reports. Erickson[6] described 11 cases of maternal rubella between 2 weeks and 2½ months of pregnancy in which the offspring showed 7 bilateral cataracts, 9 congenital heart lesions, 1 case of mental retardation and a case of possible mental retardation. He suggests that the defects were due to the greater susceptibility of embryonic tissue to virus. DuP. Guerry[7] reported 2 cases of congenital cataracts and glaucoma in which there was known rubella in the first trimester. Goar and Potts[8] added 7 cases of congenital cataracts among other defects of which 6 of the mothers had rubella in the first trimester.

Greenthal[9] reported 2 cases in which one evidenced congenital deafness and the other showed right cataract, mental retardation and a cardiac defect. Krause[10] presented 5 cases in which the multiple defects consisted of 3 premature births, 2 bilateral cataracts and 2 single cataracts, 2 showing mental retardation, one instance of bilateral total deafness and one dental aplasia. Maternal rubella had occurred between two weeks and two months.

Conte et al.[11] added 5 more cases, 4 with maternal rubella by the third month and one in the seventh month. Multiple defects consisted of cataracts (4), cardiac defects (4), mongolism (1) and cerebral aplasia (4). The authors note the difficulty of controlling the studies, i.e., the frequency of rubella in the general population and the per cent of anomalies in offspring of women who had rubella as against those who did not. On the basis of statistical evidence, they state that maternal rubella is noted in 4.2 per cent of all congenital defects which is ten times greater than the actual case rate for rubella in child-bearing age.

Three surveys of schools for deaf children provide additional data. Winterbotham[12] noted that of 48 children in an Australian school in 1945, 31 presented a history of maternal rubella in pregnancy. Eleven of these children also had murmurs. Hopkins[13] surveyed the mothers of 129 children in a school for the deaf by questionnaire. Ten mothers had rubella and two had flu between the first and second months, six in the third month, and four between four to six months. In addition to deafness, three ocular and four cardiac defects were noted. Clayton-Jones[14] examined 18 children in a selected group, i.e., no cataracts or congenital cardiac defects. There was a definite history of maternal rubella between the second and fourth month. The children were all born between August and October 1940. On checking three combined schools, 11 of 123 deaf children had a history of maternal rubella in the first trimester. The children were born between October 1940 and February 1941.

Long and Danielson[15] reported 6 cases of congenital cataract in which maternal rubella occurred between two to six weeks of pregnancy. Three of the cataracts were bilateral and 4 of the children had septal defects. All were minor feeding problems. Prendergast,[16] in a survey of pediatricians, obstetricians and ophthamologists, reported 80 cataracts, 10 other ocular defects and 32 cardiac

defects. He notes that most of the cases are in the Far West and considers the greater proximity to Australia. Altman and Dingmann[17] added a case in which there was bilateral cochlear deafness and a right congenital cataract in a child whose mother had rubella in the second month.

de Roetth and Greene[18] added 2 cases of bilateral congenital cataract in which there was a history of maternal rubella between the fifth and seventh weeks. Aycock and Ingalls[19] checked 1,300 cases of rubella in Massachusetts, and found 4 cases which had occurred during pregnancy. Two cases were in the second month of which one child showed mental retardation. The other two cases occurred in the fourth and ninth months, respectively, and both infants were normal. A restudy by Swan et al.[20] of their two original series, plus an additional series of congenital defects, led to the conclusion that there was a remarkably high correlation between the defects, especially cataracts and deafness, and maternal rubella in the first trimester.

The pathological findings to date are limited in number and conflicting in conclusions reached. Swan[21] reports autopsies on 3 infants whose mothers had rubella in the second month. Two were premature. All had a patent ductus and other cardiac anomalies. Two had cataracts which did not "exactly..... correspond to any of the large number of morphological and development lenticular opacities that have been described." The picture was one of necrosis en masse of the nuclear portion of the lens involving the primary and secondary fibers, implying a prolonged action of the etiological agent. Cordes and Barber[22] report the examination of an eight weeks embryo lens in which there was a history of maternal rubella as showing a retardation of the lens. In a later review of the subject of congenital cataracts, Cordes[23] notes that there are two types following maternal rubella—either complete opacity or a central opacity with a clear periphery. He notes that these children show an intolerance to atropine and there was an inability to dilate the pupil. Friedman and Cohen,[24] in a complete autopsy report in which the mother had a cutaneous rash (rubella?), note changes in the posterior subcapsular area, rather than in the lens nucleus. They also noted agenesis of the upper motor neurons.

Carruthers[25] considers the incidence of deaf-mutism in the origi-

nal series and suggests that there were probably more cases which were overlooked because of the early age of the infants. At autopsy, he notes the "absence of differentiation of the primitive cells to form the organ of Corti."

Evans[26] checked the teeth of the children in the original Australian series. The most striking abnormality was retardation of eruption. Of 26 children with congenital defects, 21 showed dental abnormalities, while only 2 of 8 normal children showed similar dental defects. Evans notes that the "critical" period of dental development is between the sixth and ninth weeks and the greatest number of defects occur when rubella occurs at this time.

Brown[27] attributes all defects, except those of the lens, cornea and vitreous, as being due to the effect of rubella on the fetal adrenal which supposedly influences the development of the brain and other structures.

Potter,[28] Aycock and Ingalls,[19] and Ingalls and Gordon[29] have considered the public health and epidemiologic aspects of the problem and the value of inoculation is suggested.[21, 27] The interest and awareness of the public has been noted.[30]

Acting as a damper on the enthusiastic case reports mentioned are two questions raised editorially by the British Medical Journal[31]: 1. Does the association.....arise from pure chance? 2. Was the maternal disease rubella?

Fox and Bortin[32], in a review of 22,426 cases of rubella between 1942 and 1944, found 581 females who had the disease and investigated 152 of them (roughly 25 per cent). They discovered 11 cases had occurred during pregnancy of which 5 took place up to the second month and four cases from two to four months. There was a stillborn hydrocephalic from one case which occurred in the second month. There was also a normal infant from another woman who had rubella at the same time, but who had an earlier child (1937) with bilateral cataracts. On this evidence they suggest caution in drawing conclusions.

In answer to the second question, it would seem that the material of the Australia group is highly selected so that there has probably been some tendency to neglect negative cases. Gregg, who made the original observations, was doubtful of the disease being rubella, but most American observers have felt that it is. However, making the diagnosis in retrospect is unsatisfactory and occasionally

unjustifiable. Diagnosis of congenital cardiac disease has been made on many of these cases purely on the basis of a murmur of which the interpretation is doubtful as emphasized by Miller.[33]

Changes in the activity and virulence of a virus have been known to occur. In line with this is the suggestion of Swan[34] who postulates that defects due to rubella had not been noted earlier because of a change in the virus. By a similar process future studies may show a decreased incidence of defects following maternal rubella.

Although the contention of the earlier Australian investigators that defects followed every case of early maternal rubella is undoubtedly overpessimistic, the relation of disease and defect is sufficiently great to warrant the best efforts towards prevention especially during pregnancy.

Wesselhoeft[35] suggests that exposure at an early age is generally advisable, especially in view of the mildness of the disease. This measure must be used with caution especially when there is the likelihood of pregnancy in the mother. Pooled plasma may offer temporary immunity, but it is not known how long it is effective. It is probably valueless when the disease is evident clinically as the virus has in all likelihood already reached the fetus. Since the highest incidence of the disease is in April and May, advising against conception at this time may be of value.

In the presence of threatened abortion, he advises that nothing be done to prevent the abortion. This is in line with the opinion of those embryologists and obstetricians who maintain that abortion is nature's way of disposing of a defective ovum.

Therapeutic abortion has been suggested, but legally is permissible only to save the life of the mother. Not by any reasonable stretch of the imagination can a maternal hazard be proved to be present. In a recent panel discussion on indications for therapeutic abortion[36] it was felt that there is insufficient evidence for justification of this procedure.

SUMMARY

Rubella in the first trimester of pregnancy can act on the fetus in some way and may be followed by abortion, stillbirth or various defects most frequently involving the eyes, ears, teeth or heart. The type of defect depends on the time of infection in relation to the duration of pregnancy. The defects are frequently multiple.

The frequency of defects after rubella in the first trimester is still being debated but practically all observers are agreed that the incidence is quite high.

Treatment to date is mainly prophylactic and consists of exposure early in life. The search for a practical immunization procedure is to be encouraged.

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STREPTOMYCIN AND THE PRIMARY LUNG LESION IN TUBERCULOUS CHILDREN. (Lancet, London, 1: 389, March 4, 1950).—Lorber observed the effect of streptomycin on the primary complex in the lung of 20 children with miliary tuberculosis and meningitis and of 2 children with tracheobronchial tuberculosis. It was not possible to demonstrate any beneficial effect of streptomycin on the primary complex or the symptoms attributed to it. In 8 cases tubercle bacilli persisted in stomach washings for over six months after treatment was started. It seems unwise on the present evidence to treat uncomplicated primary tuberculosis with streptomycin.—*Journal A.M.A.*

CLINICAL REVIEW

In order to encourage the writing of clinical articles by recent graduates or senior medical students, the ARCHIVES *will publish monthly at least one such paper from the classes of Doctor Reuel A. Benson, New York Medical College, New York, and Doctor Philip Moen Stimson, Cornell Medical School, New York. Other interested medical schools are cordially invited to submit student papers for consideration.*

TESTOSTERONE THERAPY IN CHILDREN*

A REVIEW OF THE LITERATURE

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The concept that the body responds as a whole to all stimuli both internal and external rather than as isolated tissues, organs or systems has achieved increased prominence during the past decade[31]. This response is particularly well illustrated during the processes of growth when any aberration in the orderly pattern of tissue accretion results in widespread alterations involving all systems. Also, since any alteration, acceleration or slow-up of the dynamic growth processes are quickly perceived, response to therapy can be easily controlled and watched. Changes, particularly in genital, neural and osseomuscular growth are reflected by early functional and anatomical aberrations. Behind these growth processes lies the interrelationship of the endocrine, metabolic and nervous functions which is a neatly balanced system.

It has been recognized by many investigators[4, 13, 30] in recent years that testosterone has widespread effects on the growing body apart from its function as a sex hormone. These effects apparently are mediated through its influence on the above interrelationship of endocrine, metabolic and nervous functions. As a consequence, it has found uses in a widening clinical sphere.

CRYPTORCHIDISM

The use of testosterone in cryptorchidism is conditioned upon the observation that there is no structural abnormality which makes descent impossible and upon the previous use and failure of chorionic gonadotropin alone.

*Submitted as partial fulfillment of the requirements of the course in Senior Pediatrics at the New York Medical College, Flower and Fifth Avenue Hospitals.

Testosterone propionate in doses of 10 mg. twice a week are tried if there is no evidence of descent by the age of 9 years. Surgical correction is advised if there are no results in 2 months and testosterone propionate is continued to correct eunuchoidism.[37]

Combined treatment with testosterone propionate and chorionic gonadotropin has been tried[29] with 53 per cent success (9 in a series of 17 showed complete descent) in a period of 3 to 12 weeks. These authors recommend that treatment should be instituted before 10 years.

Alternating treatment, using testosterone propionate 4-8 weeks, then chorionic gonadotropin 1-3 months, had poor results in a small series. Duration of treatment varied from 2-9 months[28].

The time to start therapy is a matter of dispute, though it is generally agreed to be not later than prepuberty[25]. Many men advise hormonal therapy earlier—shortly after birth (Thompson and Heckel) or at 2-3 years (Denning). Pointing up to the interrelationships mentioned above, this author[25] states that "it may be desirable to treat a child at a much younger age because of mental, physical or endocrinologic conditions that this therapy would correct or prevent.. Cryptorchid boys often become neurotic, and there may be associated behavior problems. A lack of vigor, strength, weight, muscular development and masculine characteristics may accompany deficiency of male sex hormone and improve with treatment.

In treatment of cryptorchidism per se this author felt that testosterone was merely an adjunct in that it further enlarged the parts and made descent easier. "It speeded up the results and it might cause a slightly higher percentage of cure." However, "it had a definite effect on the patients' general mental and physcial condition which was more striking than that obtained from chorionic gonadotropin alone."

HYPOGONADISM

"The basic or essential indication for administration of testosterone compounds to males is the determination of a male hormone deficiency."[29] This deficiency may vary from a slight amount to almost complete loss. It is usually associated with abdominal testes though a greater deficiency may be present with both testes in the scrotum than with both in the abdomen[7]. Primary eunu-

choidism is primary testicular failure and is treated with testosterone at the age when puberty normally sets in. Secondary eunuchoidism due to inadequate pituitary stimulation must be first ruled out with chorionic gonadotropin therapy, 500-1000 international units, intramuscularly, three times a week.[3, 7] The eunuchoid is more sensitive to the effects of testosterone than the adult with an acquired deficiency and a much lower average dose is necessary.[15, 29] Treatment of the eunuchoid patient with testosterone results in (1) gradual appearance of secondary sex characteristics, (2) remarkable increase in appetite and weight, (3) increased vigor and sense of well-being and (4) loss of female characteristics.[7]

Various schemes of treatment have been suggested for eunuchoidism. Testosterone propionate, intramuscularly 1 mg. per 5 kg. twice a week with increase or decrease as indicated, has been advocated. By the same author, methyl testosterone is administered in form of linguets for oral absorption, 1 mg. per kg. daily and 2 mg. per kg. daily for enteric absorption.[27]

Seven cases of eunuchoidism, six of them pre-adolescent, were successfully treated by implantation of testosterone propionate and methyl testosterone pellets subcutaneously. The author decided that the uniform continuous absorption from pellets was more efficient than injection in oil.[10] Successful treatment by oral therapy[11] and by inunction[12, 33] have been reported, as well as the effective use sublingually in glycol-alcohol.[5] The advantages of oral and inunction therapy in treating various hypogonadal disturbances, including infantile genitalism, atrophic testicle and eunuchoidism, are cited as effectiveness, absence of deleterious side effects, ease of administration and cooperativeness of patients.[9]

In Fröhlich's syndrome, the use of testosterone is not indicated unless both testes are in the abdomen and incapable of responding to pituitary stimulation. These conditions are not often seen in Fröhlich's syndrome. When testosterone is used it is recommended to start at the time puberty would normally start and continue until epiphyseal closure takes place.[7]

Treatment of a case of Laurence-Moon-Biedl syndrome in a 12-year-old Negro boy was carried out with testosterone. It produced growth of penis and scrotum and descent of testes but no change in eyesight or mentality.[16]

Alternation of chorionic gonadotropin and testosterone propionate was used with greater success in a series of 20 patients with underdeveloped genitalia in correcting genital hypoplasia and developing secondary sex characteristics than chorionic gonadotropin alone. "The effects of treatment upon hypogenitalism and hypogonadism were evidenced by increase in the size of the external genitalia, appearance of secondary sex characteristics and by psychological changes." Acne appeared in a few of the boys.[28]

Development of the genitals in one series[30] consisted of increase in the size of the penis, definite enlargement of testicles with normal shape and firmness. The scrotum became more pendulous and rugose. There was an increase in length of the ductus deferens and some development of the prostate. Those going through puberty had an increase in the amount of pubic hair. Three of the older boys began to have nocturnal emissions. There was no growth of pubic hair in the younger children. The rapidity of development varied greatly. "Some boys developed in 2-3 months with very small doses of methyl testosterone, whereas other boys developed slowly with larger doses. Dosage was 6-10 mg. methyl testosterone daily sublingually."

GROWTH AND DEVELOPMENT

Keeping in mind the newer concept that the body reacts as a whole to all stimuli, one is not surprised to learn that testosterone, one of the more potent stimuli, has far-reaching effects on all the tissues and systems of the body. Recognition of these effects has resulted in new clinical applications.

It was noted that large doses of testosterone propionate can cause epiphyseal union to take place more rapidly than normal. Epiphyseal age was increased 2 years over a period of 8 months by doses of 105 mg. or more per week. The danger of dwarfing resulting from overdosage to immature individuals must be kept in mind.[22] The same authors mention that 15 to 60 mg. per week were without effect on the epiphyses in eunuchoidism.

The changes anticipated at puberty when there is a natural rise in testosterone output would be a fall in calcium retention as bone growth slows markedly but a maintained positive nitrogen balance because of the growth of muscle mass and the sexual apparatus. These anticipated changes were demonstrated in 5 pre-puberal

boys with methyl testosterone. Administration of the hormone resulted in increased calcium excretion and a maintained nitrogen balance.[28] Positive nitrogen balance without a rise in non-protein nitrogenous components of the blood points to increased protein formation which is evidenced by the increased muscle mass.

Correlation between the excretion of 17 ketosteroids and creatinine in growing boys and girls points to a fundamental relationship.[33] These authors conclude that androgens have an influence on muscle mass so that an increase of androgen formation results in increased muscle mass.

Widespread metabolic effects of testosterone have been demonstrated, such as raising of basal metabolic rate and lowering of respiratory quotient, which was equivalent to increased oxidation of fat.[13]

As with other steroids, testosterone also decreased the excretion of electrolytes and water. The retention of phosphorus and nitrogen with concomitant increase in musculature resulted in increased physical endurance and capacity for muscular work in hypogonadal patients. In addition, there was a marked increase in the red blood count and hemoglobin in eunuchoids, a decreased vasomotor instability and increased velocity of blood through surface vessels. Of the many methods of administration, these authors[4] felt that methyl testosterone by mouth was particularly effective for growth and development.

The oral treatment of 2 hypogonadal boys with 30-50 mg. methyl testosterone daily for 41 and 57 days resulted in rapid growth and development of genitalia and body as a whole with an increase in weight and height.[2]

The treatment of 6 cases of primary testicular failure with 25 mg. of testosterone propionate three times a week resulted in an increase in total weight, a decrease in mammary and abdominal fat and growth spurts during periods of administration. There was no x-ray evidence of epiphyseal closure.[3]

Doses up to 75 to 125 mg. weekly of testosterone propionate in 8 hypogonadal adolescent boys, ranging from 9-18 years, were accompanied by an increase in average growth rate from 1.36 cm. per 100 days during control period to 3.6 cm. per 100 days during treatment period. Rate fell to 1.56 with cessation of therapy. X-ray of knees, ankles and wrists taken at beginning and end of

therapy showed no evidence of epiphyseal change. However, the authors[17] point out that the use of testosterone propionate as a growth stimulant in a normal adolescent might result in permanent epiphyseal damage.

An acceleration of statural growth in 3 adolescent hypogonadal boys treated with testosterone propionate at weekly intervals for 3-6 weeks has been reported.[18] A growth of 4 cm. during 6 months treatment of a 21-year-old with large doses of testosterone propionate has also been reported.[19]

Consideration of testosterone as a general growth hormone is supported by its effect on the genital tract, musculature, hair growth and skin changes (thicker, more hyperemic and velvety).[19] These authors treated a case of pituitary dwarfism with desiccated thyroid, polyvalent anterior pituitary extract, pregnancy urine extract and pregnant mare's serum extract with no increase in the size of the genitalia or signs of maturity. Highest growth rate achieved was 1¾ inches a year. Following administration of methyl testosterone there were marked signs of maturity and the growth rate went up to 3.9 inches per year.

The use of testosterone to promote growth in pituitary dwarfism has been recommended under certain specified conditions.[7] It should be used only if both testes are in the abdominal cavity and are unable to respond to chorionic gonadotropin. This is not often the case in pituitary dwarfism. This author further states that treatment with testosterone and chorionic gonadotropin should not be started until about the twelfth year to avoid too early aging and closing of epiphyses.

Treatment of hypopituitarism, as suggested by another author,[17] should include methyl testosterone orally in doses of 5-10 mg. on arising and 5-10 mg. at bedtime with adjustment of dose according to virilizing effect. In the case of pituitary dwarfism, this author states that small doses (10-15 mg.) may be given over a long period of time (2-3 years) without fear of excess virilizing effects and without producing premature closure of the epiphyses. However, in females sometimes even small doses have persistent effects on the vocal cords and facial hair growth.

Hypogonadal dwarfism has been treated in boys below age of pubescence with 10-20 mg. of methyl testosterone daily if there is failure to gain a response with chorionic gonadotropin. In boys

with delayed development at the time of puberty the dose is 25 mg. twice a week to a total of 300-500 mg. depending on growth response. Treatment may be continued intermittently in accordance with the progress of growth.[27]

The response of the body to a potent stimulus, such as testosterone, depends on the state of balance which has been struck in the interrelationship of metabolic, endocrine and neural functions as mentioned above. Doses which produced growth in cases of genital infantilism and retarded growth in one patient, arrested excessive eunuchoidal growth in another patient.[14] This latter patient, a 14-year-old male, was treated with 25 mg. of testosterone propionate twice a week plus 10 mg. methyl testosterone twice a day until a total of 625 mg. had been given.

Testosterone propionate alone was used to decrease the growth rate in a case of gigantism.[1]

One further clinical use of testosterone which apparently stems from its salutory effects on tissue metabolism is the treatment of dermatomyositis.[25] Satisfactory results have been obtained by the implantation of 3 or 4 testosterone pellets of 75 mg. size or by methyl testosterone orally 5-10 mg. daily.

PREMATURITY

The high mortality of premature infants has been ascribed to general immaturity of the tissues and organs, when more overt causes, such as hemorrhage, respiratory failure and infection can be ruled out by autopsy. Consequently, the production of rapid tissue and organ growth should have distinctly beneficial results in lowering the death rate among prematures.

The importance of the nitrogen-storage effect of testosterone was recognized and the hormone was administered to prematures with edifying results.[6] Fifteen premature infants weighing less than 2,000 grams were given 2-5 mg. of methyl testosterone in their feedings every 12 hours over a period of 4-7 weeks. Predictable mortality for this group was 50 per cent. However, all 15 survived. The initial weight loss was minimal and weight gain and vigor were initiated early. The hormone was given to both sexes. There were no untoward effects.

In a follow-up paper, these authors extended their work in greater detail.[21] Using as an index the days required to regain birth

weight and days required to reach 2,500 grams, the authors presented the following interesting comparisons:

Average days required to regain birth weight:

Babies weighing at birth	Control	Methyl Testosterone	T. Propionate
1000-1500 gms.	14.7	7.5	7.5
1500-2000 gms.	11.9	7.8	9.8

Average days required to reach 2500 grams:

Babies weighing at birth			
1000-1500 gms.	58.8	56.9	55
1500-2000 gms.	42.1	32.6	35.1

Regain and maintenance of birth weight might be explained by retention of sodium, chloride and water but no edema was noted and no sharp weight loss was seen after withdrawal of hormone.

It is now generally accepted that testosterone causes a decline in urinary nitrogen without an increase in plasma protein, non-protein nitrogen, blood urea nitrogen or hemoglobin. This suggests to the authors that tissue building is the cause of this nitrogen decline. With the dosages used there should be no effect on the epiphyses.[22] The authors[21] conclude that testosterone has definite use as an adjunct in the cure of selected prematures needing a metabolic stimulus, but they do not advocate its routine use. No contraindications were specified.

ENURESIS

The problem of enuresis has been handled in the literature from many standpoints, including urologic, psychologic, neurologic and metabolic. Therapy has also, as a rule, started from one or more of the above orientations with varying degrees of success. Perhaps the recognition that enuresis is an expression of unbalance of many systems of the body may produce new and better results.

The specific effects of male sex hormone on the developing male genitourinary system have been stated as follows: it "lengthens the urethra, enlarges the prostate, and increases the bladder and sphincter musculature. Therefore the child has greater urinary capacity and better control. Essentially, the same transition occurs at puberty, during which time enuresis undergoes a spontaneous cure."[23]

The condition of familial enuresis has been explained and

treated with testosterone[23] and warrants inclusion here as it points out well the action of the hormone. "Unintentional and unconscious diurnal or nocturnal discharge of urine may be a Mendelian recessive trait." It is inherited as a behavior pattern from the parent or grandparent whose lower half of the body the child favors. One-third of patients with urinary incontinence after the third year of life have this familial defect.

The normal child responds to training so that as the immature neuromuscular bladder mechanism achieves somatic maturation, the child will respond with improved and finally complete control. In enuresis the infantile condition persists and the detrusor continues to overcome the sphincter. As a rule enuresis clears spontaneously at puberty when sexual maturation strengthens the action of the sphincter; however, the adult may still remain subject to urinary incontinence.

This study included 75 otherwise normal children of familial enuretics with and without emotional and training problems who had failed on all forms of therapy.

Treatment consisted of 10-30 mg. methyl testosterone orally and intramuscularly per day along with a restricted fluid regime and psychotherapy. Nocturnal enuresis diminished in frequency and urgency in 3-10 weeks. The author concluded that the androgenic material gave more confidence and less anxiety about bladder control. The results were 59 cured, 10 improved and 6 failed.

Another author[8] treated 50 enuretic children (3½-14 years) with intramuscular (10-25 mg. testosterone propionate in oil daily) and topical applications (8 mg. per day). Of 14 girls, 7 were cured, 6 improved and 1 unchanged. Of 36 boys, 20 were cured, 11 improved and 5 unchanged. Hence 54 per cent were completely cured, 34 per cent much improved and 12 per cent unchanged.

EMOTIONAL IMMATURITY AND BEHAVIOR PROBLEMS

"The close relationship between the endocrine system and neuropsychiatric functions is being more and more recognized."[24] The question arises as to whether there is a common genetic factor explaining both the endocrinopathies and the behavior problems which are seen in the same children. Personal observations of

one investigator[28] suggest that the psychic abnormalities are a result of many traumatic nervous experiences which are heaped on the child because of his endocrinologically-determined somatic deficiences. He becomes the butt of the jokes of his fellows and a target for abuse and ridicule all of which has far-reaching psychological effects.

On the other hand, this author continues, "anxiety, depression and emotional instability frequently accompany diminished sexual drive whether organically or psychically determined," and further "it is known that behavioral difficulties may be favorably influenced by testosterone propionate."

In the series of cases presented by this author it appeared that "the most frequent and probably basic cause for behavioral aberration which in many instances upset the individual and also caused him to become a social problem was an inadequate adjustment to the feelings of being different." This "being different" led to a variety of psychic mechanisms including inferiority, inhibitions, conflicts, etc. Each child reacted individually to his deficiency, some being aggressive, some submissive, etc. The author found no relation of behavior problem to body type such as eunuchoid or Fröhlich's.

The cases were successfully treated with testosterone and dosage varied with the degree of structural deficiency, for example, well-marked hypogonadism was treated with 25 mg. three times a week.

A carefully selected group of 58 children between the ages of 7 and 15 years were treated with methyl testosterone sublingually in total daily doses ranging from 6-10 mg.[30] All of the patients had small genitalia. The fat mons often covered the penis causing urination to be difficult and embarrassing. The overtones of this condition permeated the entire personality of the patient. "All of the children and their parents believed that the condition was abnormal and that improvement in size was desirable if it could be obtained. Several of the children had a neurosis wholly or partly due to the cruelty of the other children laughing or making remarks about the infantile nature of their organs. Many boys were emotionally immature or physically weak. Some complained of enuresis. Failure in school or very poor work in spite of good intelligence was often reported."

Results of treatment were seen in growth of genitals, increased rate of growth of the child and physical improvement with increased muscular development and stamina. From an emotional standpoint, there were "noticeable improvements—in the lessening of the feelings of inferiority; the children cooperated better with parents and teachers and took more responsibility. They were less inclined to act like younger children and became more amenable to reason, showing an improvement in their personalities." A general psychological maturation was noted. Children were able to concentrate better and their school work improved.

SUMMARY

Suggestions were made concerning the significance of the widened clinical sphere of what was formerly a hormone of sexual function.

The use of testosterone in cryptorchidism, hypogonadism, growth and development prematurity, enuresis and emotional problems was reviewed. Its salutory effects in producing somatic maturation of the genito-urinary system, stimulation and growth of all tissues, and emotional maturation were strikingly noted.

The methods of administration and dosages used by a variety of investigators were reported. Good effects resulted from oral, intramuscular, percutaneous and sublingual administration.

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TUBERCULOUS INFECTION IN ELEMENTARY SCHOOL. (British Journal of Tuberculosis, London, 44: 1, Jan. 1950). Jones Davies surveyed the incidence of tuberculous infection in the elementary school children of a rural county in Wales, the sources of such infection and the contributory social and other possible factors. The presence of tuberculous infection was detected by patch test, using double strength tuberculin jelly as prepared by Jensen, a modification of the method described by Mourad. A preliminary investigation showed that the tuberculin patch test was 100 per cent reliable when compared with the Mantoux test. The incidence of tuberculous infection was 6.5 per cent. Seventy-six per cent of reactors were found to have been in direct contact with a person who had pulmonary tuberculosis. Investigation of the sources of contact infection showed that tuberculosis is a highly infectious disease but spread of tuberculous infection of the human type did not occur within the schools. The incidence of tuberculous infection bore no relationship to poor housing, bad sanitation, nutritional state, high rainfall, low mean temperature, low number of sunshine hours, exposure to rain-bearing winds, geologic formation or susceptible anthropologic types. The author cites other reports indicating that poor housing has no relation to the incidence of tuberculosis. It is the number of infecting foci in a slum area that is the most important factor. Housing becomes important only when healthy persons are compelled by overcrowding and bad ventilation to inhale massive doses of germs. The maintenance of the optimum nutritional state is next in importance to the removal of the infecting reservoir in the prevention of the onset of tuberculous disease. Fatigue is equally detrimental to bodily well-being. Good feeding, however, will do much to allay the onset of fatigue.—*Journal A.M.A.*

PEDIATRICS HALF A CENTURY AGO

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

CHRONIC DIFFUSE NEPHRITIS*

Report of Case in a Four-Year-Old Boy With A Rudimentary Kidney.

A. C. Cotton, M.D.
Chicago, Ill.

The rarity of solitary kidney is evident from the limited number of cases found on autopsy. Holt mentions but one case of single kidney in a thousand consecutive autopsies, in which twenty renal malformations were found. Ziegler says: "Congenital atrophy of one kidney is more common than entire absence. In well marked cases the atrophied kidney appears as a thin plate of fibrous tissue 2 to 5 cm. in length and 1½ to 3 cm. broad, with few or no traces of tubules or glomeruli, and is supplied by renal vessels normal in position but abnormally small."

G. B. Fowler states that in 11,978 autopsies made at the four largest London hospitals only three instances of marked atrophy were observed and that in 1894 not more than 70 or 80 cases had been reported. From an analysis of a large number of autopsies Morris concludes that single kidney is found only once in 2,400 bodies. Ballowitz, in Virchow's Archives, August 5, 1895, reports as a result of his researches 213 cases of absence of kidney.

Etiology. As to the etiology of this interesting condition Ziegler states: "The causes which determine the non-development of one of the kidneys are unknown. We can only say that for some reason the outgrowth from the primitive ureter out of which the kidney is fashioned has been hindered or altogether suppressed. In some cases, however, traces of inflammation in the form of cellular infiltration and fibrous hyperplasia are discovered in the rudimentary organ. We are thus led to infer that intrauterine inflam-

*Read before the Fifteenth Annual Meeting of the American Pediatric Society held at Washington, D. C., May 12-14, 1903.

Reprinted from Archives of Pediatrics, 21: 241-249, April 1904.

mation of the kidney is possible and may lead to arrest of its development."

The American Text-Book of Pathology suggests that renal hypoplasia may be due to faulty development, to congenital smallness of renal artery, to intrauterine inflammatory changes or to congenital stricture of the ureter. Although it has been stated that we have twice as much renal parenchyma as is necessary to carry on elimination, the statement may well be questioned from the fact that reported cases of hypoplasia of a kidney show compensatory hypertrophy of its fellow. Our autopsy shows no exception to this rule, the single kidney showing marked enlargement.

It is not strange that half the cases of absence of one kidney show a tendency to disease in the remaining organ. That the gravity of nephritis, either acute or chronic, should be manifold in these patients is self evident.

The following report embodies the history of a case in a boy of four years who had a rudimentary kidney.

CASE REPORT

Family History. Father living and well, has four brothers and one sister all healthy. Mother living and well, has three brothers and four sisters, all healthy. Patient has three sisters, two healthy, one with infantile cerebral paralysis. One brother died of cholera infantum and one sister died ten days after birth.

Personal History. Was a normal baby. First severe illness was in October 1900, when he had an attack of bronchopneumonia, lasting twelve weeks. Since then has never been strong, catching cold readily. During these colds the mother noticed the urine decreased in quantity, was often passed involuntarily and was of an ammoniacal odor. In January 1902, edema of ankles and lower lids first appeared, disappearing and recurring at varying intervals under treatment. The child had measles in April 1902, after which there was first observed the distention of the abdomen which still persists.

Physical Examination. Child is fairly nourished. Eyelids are closed by edema. Abdomen is distended and fluctuating. Ankles edematous. All other points negative. Slight cough without physical signs.

Urine. Examination of twenty-four hours' specimen of urine

showed the total amount to be 480 c.c.; specific gravity, 1,012; urea, 1.6 per cent; urea, total, 7.68 gm.; total solids, 12.8 gm.; albumin present; hyaline and granular casts present.

Treatment and Record. The patient was put to bed, placed on liquid diet and freely supplied with water and lemonade. Morning and evening he was given hot baths, followed by thirty minute hot packs which usually caused abundant diaphoresis. Citrate of potash was administered in small doses and later normal salt enemata were employed for diuretic effect.

This treatment, varied to suit the symptoms, was continued until the middle of October. Under it the patient would improve for a time, the edema and ascites would almost disappear and he was allowed to sit up and even walk about the ward. Then, suddenly, edema would appear, the pulse and respiration would become accelerated with a slight rise of temperature. During this period the patient urinated from eight to twelve or more times each day, always in small amounts. The total amount varied from 300 to 900 cc. for twenty-four hours and the specific gravity from 1,007 to 1,013. Albumin was always present in considerable amount; urea percentage was low and the total urea was small.

The temperature ranged from 98° to 100° F., occasionally reaching 100.5° or even 101° F. The pulse rate varied from 90 to 150, usually ranging between 110 and 130. The pulse was often weak and sometimes irregular.

During the latter part of August an eczematous rash appeared on the head and face, to a lesser degree upon the body and limbs, and persisted for several weeks. On September 15 the patient had improved so much that he was given light diet in place of the liquids. His medicine consisted of carbonate of ammonia in 2 grain doses; diuretin in 5 grain doses four times a day, and magnesia sulphate in 2 dram doses each morning.

From October 10 to 20 the patient was troubled with vomiting and pulse was often irregular and weak. He was again put on liquid diet and given diuretin in 5 grain doses, with strychnia, 1/120 gr., four times daily. On October 22 calomel, in doses of 1/10 grain every two hours, was ordered, and magnesia citrate, 2 ounces, given every morning. The result of the treatment was quite a severe salivation which began on October 25, with a rising temperature, which reached 102° F., and gradually subsided by

the twenty-ninth. The pulse ranged from 120 to 160, was weak and often irregular. The teeth were slightly loosened, tongue and lips much swollen; face and eyelids markedly edematous. The submaxillary and parotid glands were enlarged and tender; the breath was foul and lips excoriated.

About December 15 the patient developed some impetigo contagiosa which proved unusually obstinate. The general symptoms again improved and he was given a soft diet. Sweats were ordered once instead of twice daily. Until February 1903 nothing occurred; the patient was better and worse at intervals, with a general downward tendency.

On February 10 a morning specimen of urine showed a very large amount of albumin, many hyaline and granular, and a few waxy casts. The temperature began to show a subnormal tendency, frequently as low as 97° F., by rectum, with a diminution in the amount of urine. Urination was frequently involuntary, so that the total amount could not be accurately determined. February 14, while the ward was being fumigated, the patient was transferred to a room on the sixth floor of the hospital in which, during the extremely cold weather that followed, a proper temperature could not be maintained. The sweats were necessarily discontinued and the child grew rapidly worse. On February 18 he urinated only three times, a total of 180 cc. The urine was loaded with albumin. The specific gravity was 1,010, with a few hyaline and many granular and fatty casts. The following day he passed urine twice, a total of 112 cc., and on the twentieth there was almost complete anuria. During these three days the patient was much prostrated with tendency to semicoma. Physical examination showed considerable fluid in the abdomen and lower part of the thorax. Auscultation revealed large numbers of moist râles throughout the lungs. Respiration was rapid (40 to 60 per minute), labored and apparently painful. The breath was heavy with a urinous odor. The temperature was subnormal and pulse weak and irregular, ranging from 100 to 156. Muscular twitchings and tremor began on the eighteenth, but no general convulsion occurred. On the twentieth the patient was returned to the children's ward and given a hot bath with no apparent effect. The pulse became extremely rapid; the respiration shallow and the patient died at 2:30 P.M., two and a half hours after the bath.

During this patient's nine months residence in the hospital his urine was examined 100 times, nearly forty of these examinations being twenty-four hour specimens in which the total amount, specific gravity, percentage of urea, total urea, total solids and albumin, were carefully estimated. The table of findings is reduced to general average as follows:

	Total amount of Urine	Specific Gravity	Urea, per cent	Urea Total	Total Solid
Average.....	623	1,010.8	.759	4.87	14.29
Highest.....	1,200	1,018	1.6	18.00	32.48
Lowest.....	300	1,006	.5	1.80	7.00

AUTOPSY RECORD

Necropsy of C. B. C., age four years, performed by Peter Bassoe, M. D. Date of death, February 2, 1903. Date of autopsy, February 2, 1903; clinical diagnosis, chronic nephritis.

External Examination. Child well nourished; skin pale; slight edema of legs and chest; rigor mortis slight; small abrasions on right index finger and thumb; length of body one meter.

Internal Examination. Subcutaneous fat 1 cm. thick; peritoneal cavity contains one liter of clear serous fluid; peritoneum smooth and presents no abnormal adhesions; liver extends 3 cm. below costal arch in right mammary line. There is a large Meckel's diverticulum.

Thorax: Each pleural cavity contains 250 cc. of straw colored fluid. On the right side are a few frail bands of adhesions uniting the parietal pleura with that covering the lung. The left side is free from adhesions. The pericardium contains 2 ounces of clear fluid. The thymus gland: In its position is a thick layer of fat in the centre of which is a firm tissue. The thyroid gland: Size proportionate to age. Glistening, pale grayish red on section. Larynx: Mucous membrane smooth and pale. Trachea: Mucous membrane smooth and pale; tracheobronchial lymph nodes a little enlarged and pale red in color.

Lungs: Left, weight 120 gms.; bluish gray and smooth externally; floats in water. Upper lobe crepitates freely; on section reddish, but contains very little blood; tissue tough, permeated by heavy bands of fibrous tissue. Lower lobe a little darker on cut surface, otherwise the same in appearance as upper. Right, weight 130 gms.; floats on water; fissure between upper and mid-

dle lobes partly obliterated. Upper and lower lobes very firm and crepitate very feebly. Middle lobe crepitates freely. On section the right resembles the left lung closely, except that in the lower lobe a little mucus can be expressed from the smaller bronchi.

Heart: Weight 130 gms. Contains small amount of fluid blood. Tricuspid opening admits three fingers and mitral opening two. All the valves are smooth. Left ventricle is 6 cm. long; ventricular wall 1 cm. thick. Right ventricle is 5 cm. long; wall is 2 mm. thick. Circumference of aortic opening is 44 mm.; of pulmonary opening 45 mm. Foramen ovale is closed. Myocardium is pale.

Mouth and pharynx normal on inspection, esophagus smooth.

Abdomen: Spleen, weight 50 gms.; externally light reddish in color; cuts with increased resistance; trabeculae prominent on section.

Stomach: Size proportionate to age, contains some sour smelling milk curds; mucous membrane smooth and of normal appearance.

Small Intestine: Lining is smooth throughout. 80 cm. from ileocecal valve is a Meckel's diverticulum 6 cm. in length and as thick as the index finger; no constriction at base; at free end are two shallow pouches containing a small amount of mucus. Appendix: 9 cm. in length, normal in appearance.

Large Intestine: Solitary follicles prominent, especially in upper part; mucous membrane smooth throughout.

Pancreas: Weight 30 gms.; cut surface pale; markings are distinct.

Liver: Weight 550 gms.; external surface smooth, pale; cuts with slightly increased resistance; cut surface pale; small amount blood; lobular markings very distinct. Gall bladder contains thick greenish bile; walls thicker than normal.

Adrenals show no changes; both of usual size.

Right Kidney: Weight 65 gms.; length 7 cm., width 4 cm., thickness 3.5 cm. The perirenal fat is considerable in amount. The capsule strips easily but leaves a very irregular surface with prominent stellate veins and many minute depressions and elevations. Cut surface is a mottled light grey. Cortex is pale, the distinction between cortex and medulla very slight. Cortical markings are very distinct. Mucous membrane of the pelvis is smooth.

Left Kidney is rudimentary, and consists of a small triangular whitish body with base upward. It measures 1 cm. in width and 1½ cm. in length. From this body an artery and a vein can be traced to the aorta and ascending vena cava, respectively.

Right ureter normal in size and position. Left ureter, length 13 cm.; inserted into bladder in normal position; terminates above in the rudimentary left kidney described. The ureter possesses no demonstrable lumen.

Bladder, prostate, testicles and seminal vesicles normal. The epiphyseal cartilage at the lower end of the femur is 1½ mm. thick; line of ossification perfectly regular.

Anatomical Diagnosis. (1) Extreme hypoplasia of left kidney. (2) Chronic diffuse nephritis (right kidney). (3) Hydroperitoneum. (4) Hydrothorax. (5) Hydropericardium. (6) Edema of legs and thoracic wall. (7) Hypertrophy of left ventricle. (8) Slight bronchitis. (9) Fatty liver. (10) Peristent Meckel's diverticulum. (11) Chronic interstitial pneumonia. (12) Hyperplasia of solitary follicles of ascending colon. (13) Localized fibrous pleuritis.

Histologic Findings. Only those concerning the kidneys will be given.

Right Kidney: A great many of the tubules are dilated and contain hyaline masses. Other tubules contain leukocytes and epithelial debris. In the cortex and more so in the pyramids are found accumulations of round cells many of which are polymorphonuclear leukocytes. In the cortex are hyaline fibrous glomeruli. The condition is one of acute inflammation engrafted on a chronic diffuse nephritis.

Left Kidney: The rudminetary left kidney was cut in serial sections, made horizontally, if we imagine the kidney in its position in the erect body. Each group of ten sections was placed in a separate numbered bottle and two or three sections of each stained by hematoxylon and eosin. The numbers used in the following description apply to these fifty-five groups, each roughly representing 1/55 of the length of the kidney.

Nos. 1 to 4: Sections are made up of a dense fibrous tissue with scant elongated nuclei, and considerable evidence of hyaline degeneration. In No. 4 is a straight row of rounded nuclei which suggests a tubular structure which become plain in No. 5. In

No. 6 and No. 7 the hyaline degeneration becomes more pronounced. In No. 8 we see a cross section of a tubule the diameter of which is a little more than half of that of a normal glomerulus. It is lined by a single layer of low epithelium and contains homogeneous material which takes a pink stain, and may be said to constitute a hyaline cast. In No. 9 two structures are seen which appear to be imperfect glomeruli. In No. 10 and 11 a couple of additional tubules are seen in longitudinal section.

Beginning with No. 7 a rather large space has been noticed in the interior of all sections. In No. 12 it is plainly seen to be lined by a single layer of flat epithelium. It is narrow but extends over more than the central half of the section. The latter measures 10x12 mm. This space contains a homogeneous faintly stained material.

In the succeeding sections several new tubules are encountered some of them lined by a tall cylindrical epithelium. In No. 15 several such tubules of the convoluted type are seen in longitudinal section, but there are no glomeruli. In No. 17 is a glomerulus-like structure which is partly calcified. Near it are several fairly well-formed tubules of convoluted type. From No. 25 downward the tubular structures diminish in number and the central space becomes smaller and indistinct. The sections mainly consist of hyaline fibrous tissue, with a few tubules surrounded by a more cellular connective tissue and a number of thickened blood-vessels.

In No. 32 the tubules again become more numerous. In No. 35 is a small collection of mononuclear round cells around a group of tubules. In No. 48 the interior cavity and its epithelial lining become plainer and persist to the last section (55). In all sections the blood-vessels are quite numerous, except in the hyaline interior portion, and their walls are thickened. The cavity mentioned as occupying the interior of most of the sections may represent the pelvis or possibly merely a cyst. At no point were tubules seen to empty into it.

DEPARTMENT OF ABSTRACTS

MASSELL, B. F.; WARREN, J. E.; STURGIS, G. P.; HALL, B. AND CRAIGE, E.: THE CLINICAL RESPONSE OF RHEUMATIC FEVER AND ACUTE CARDITIS TO ACTH. (New England Journal of Medicine, *242*:641, April 27, 1950, and *242*:692, May 4, 1950).

ACTH was administered for periods of ten days to fourteen weeks to 10 patients with active rheumatic fever. At the time ACTH therapy was begun, 8 patients had definite fever, 7 had joint symptoms, 3 had subcutaneous nodules, 1 had chorea, 9 had signs of valvular involvement, 4 had pericarditis, 4 were in congestive failure, and all but one had elevation of Erythrocite sedimentation rate. The marked variability of the course of rheumatic fever necessitates postponement of the final value of ACTH. However, the response of most of the patients treated with ACTH has been such that it is difficult to disregard the indications that this hormone often causes a marked suppression of rheumatic activity and even shortens the course of the disease in some cases. The clinical response was satisfactory in all but one of the ten patients. The patient who did not respond was a 7-year-old girl who was extremely ill with subcutaneous nodules, severe valvular damage, cardiac enlargement and congestive failure. There is, at present, no reason to believe that patients who have recovered from an attack of rheumatic fever after ACTH therapy are any less likely to have rheumatic recurrences than patients who have spontaneously recovered from the disease. Of all the manifestations, fever and polyarthritis came under control the most rapidly. Definite elevation of the temperature which was present in 8 cases subsided in 24 hours in all but one, in which it subsided after 48 hours of therapy. Arthritis was present when ACTH therapy was begun in 7 cases and completely cleared up within 1 or 2 days in 5 of these. The remaining 2 patients, although much improved within 24 hours, required 3 to 4 days before their joints became entirely normal. Pericarditis was present in 4 patients, 3 of whom also had effusion. In the one case without effusion, all physical signs of pericardial involvement disappeared within 24 hours of therapy whereas in the other three cases the signs disappeared in 3, 11 and 14 days, respectively. Multiple subcutaneous nodules

were a prominent part of the disease in 3 patients. In two cases improvement was noted in 7 to 10 days while in the third case the nodules became smaller very gradually and did not disappear until 3 weeks after termination of therapy. Only one case had chorea. Although ACTH was given for a total of only 10 days, the improvement and final abatement of the chorea was striking. Improvement in appetite and gain in weight with ACTH therapy and improvement in anemia was frequently impressive and often remarkably prompt. In several patients, who had a marked sinus tachycardia, there was considerable slowing of the heart rate soon after ACTH therapy was begun. The response of those with congestive heart failure and the disappearance of murmurs following ACTH therapy is quite a remarkable finding. Some of the untoward reactions to ACTH therapy include the tendency to retention of fluids which is a factor to be considered in those patients with congestive heart failure, mental depression, headaches, acne and varying degrees of roundness of the face. The evidence suggests that the effect of ACTH in rheumatic fever is indirect and depends upon stimulation of the adrenal cortex and a consequent increased production of 11, 17-oxysteroids. However, the way in which the adrenocortical steroids suppress the inflammatory rheumatic process is still not understood.

MICHAEL A. BRESCIA, M.D.

GOTTLIEB, C.; CHU, F. AND SHARLIN, H. S.: PERFORATION OF A GASTRIC ULCER ASSOCIATED WITH INTRACRANIAL HEMORRHAGE IN A NEWBORN INFANT. (Radiology, 54: 595, April 1950).

The infant reported by the authors was the second child of a Puerto Rican mother born spontaneously after a normal prenatal course. Birth weight 6 pounds 14 ounces. The infant appeared well until the second day when he passed two dark red stools and vomited dark brown fluid once. The physical examination was negative except for skin pallor. Later the same day the infant had another bloody stool and appeared weaker and paler. The next morning the infant was given some barium milk for x-ray study. X-ray studies revealed a large filling defect in the cardiac end of the stomach on the greater curvature, marked gaseous distention of the small intestine, free air under the domes of the diaphragm and a fluid level in the peritoneal cavity. On surgical

exploration a large amount of gas and fluid was found in the peritoneal cavity. A perforation surrounded by a necrotic ulcer was seen on the anterior wall of the stomach. A large blood clot plugged the perforation (corresponding to the filling defect). The blood clot was removed, the ulcer excised and the perforation was closed. The infant withstood the procedure well but died suddenly 16 hours after the operation. The post-mortem revealed the stomach in good condition but there was a tear of the tentorium with a few cubic centimeters of free blood between the brain and the tentorium. In view of the work of Cushing and others, who have found that melena in infants may be attributable to an intracranial lesion, the findings in this case must be considered as an example of such a relationship, rather than as coincidental.

MICHAEL A. BRESCIA, M.D.

LINKER, M.; ROSENTHAL, I. M. AND GOLOMB, J.: TETANUS RESULTING FROM A FOREIGN BODY IN THE NOSE. (New York State Journal of Medicine, 50:1620, July 1, 1950).

This is a case of a 17-month-old negro male child who was admitted to the hospital with a five-day history of difficulty in swallowing. The admission examination revealed a well-developed infant in acute distress with noisy and irregular respiration and a profuse purulent discharge from both nostrils. The mouth could not be examined because of a trismus. The patient's nose was aspirated following which he was more comfortable and was able to sit up and drink a bottle. After a fairly comfortable night the child was noted to be slightly dyspneic. Much mucopurulent material was aspirated from both nostrils and finally a paper matchstick was aspirated from the right tonsil. Cultures from the discharge and matchstick at first revealed staphlococcus and E. coli but later C. tetani were recovered. By this time the diagnosis of tetanus was strongly suspected and then confirmed by the positive culture of C. tetani. However, in spite of specific therapy and sedation the infant died with tetanus. This case illustrates the possibility of developing tetanus from a contaminated foreign body in the nasal passages.

MICHAEL A. BRESCIA, M.D.

HARVEY, R. M.: WILMS' TUMOR—EVALUATION OF TREATMENT METHODS. (Radiology, 54:689, May 1950).

Wilms' tumor comprises 20 per cent of all the malignant tumors in infancy and childhood, 75 per cent of the cases occurring before 5 years of age. They are characterized by their lack of symptoms. The one constant and outstanding feature is the presence of an abdominal mass which is usually discovered accidently at a routine examination. Less common symptoms are fever, gastro-intestinal complaints and disturbances of urination. Pain is uncommon and is usually manifested as a dragging sensation due to the weight of the mass. The diagnosis is based on the finding of an abdominal mass in an infant and elimination of other possible causes by intravenous and retrograde pyelography. Five basic plans of treatment of Wilms' tumor have been advocated and practiced. These include irradiation alone, surgery alone, preoperative irradiation plus surgery, surgery plus postoperative irradiation and preoperative irradiation, surgery and postoperative irradiation. The author feels that the last of these is the best method of approach and feels that a large series of cases should be given the benefit of preoperative irradiation in addition to surgery and postoperative irradiation. These cases should be so-called operable cases and not hopeless cases. MICHAEL A. BRESCIA, M.D.

KAPLAN, M.: AN APPROACH TO PSYCHIATRIC PROBLEMS IN CHILDHOOD. (American Journal of Diseases of Children, 79:791 May 1950).

Child psychiatry is often only the conscious application of common sense principles to the difficulties parents and children encounter in living with each other. Understanding the psychiatric problems that occur in children is an adequate conception of the nature of the psychologic growth and development of a child from birth until biologic maturity. There are two biologically determined forces operating within him, viz., dependence and independence. There is a constant interplay of these two forces throughout the developmental period. In the very young child one may see an insistence beyond the usual age on drinking milk through a nipple and at the same time an equal insistence on his own handling of the spoon with which he is fed more solid foods. It should be noted that the period of relative dependence varies with the culture into which the child is born. In some cultures a child is able and is expected to care for most of his needs by early adolescence. In our own culture the period of relative dependence often continues

even past adolescence. It might be stated that most if not all, of the emotional problems of children have their roots in the dynamic relationship of these two forces as they operate within the parent-child constellation. It should be stressed that emotional problems in children occur when something has gone wrong in the relationship between the child and his parents. The child is a delicate barometer reflecting the state of feeling within the family. Thus difficulties in the child become clear only when the conflicts within either one or both parents begin to be understood. The earliest and perhaps the most important relationship between mother and child occurs in feeding. Through the feeding experience the basic pattern of the relationship between the mother and child becomes established. This is mediated through the developing sensory apparatus of the child: touch, smell, taste, kinesthetic sensation, sight and sound. The next important period during which a conflict situation may develop between the infant and his mother is at weaning. In addition to understanding the mother's attitudes regarding weaning, it is also necessary to recognize what the child may be expressing by his reluctance to give up his nursing. Another important event in the child's life over which a conflict may occur is when toilet training is undertaken. A former rigid approach has given way to a more tolerant view toward toilet training. Thus one may consider the individual differences in the rate of maturation and to suggest to the parents that they themselves observe and judge the child's readiness for training. The preschool and early school period is another time that problems may occur. Where previously the child generally reacted to the parents as though they were omniscient and omnipotent, he now expresses more frequently and more definitely his growing doubts regarding their power and wisdom. If the basic relationship between the child and the parents has been good, it is not likely that any serious problems will occur. If, however, the intrafamilial relationships are disturbed and there is a conflict, not only between the parents and the child but between the parents themselves, then such disturbances are apt to be accentuated by the problems presented at this time. MICHAEL A. BRESCIA, M.D.

HUGHES, J. G.; HILL, F. S. AND DAVIS, B. C.: ELECTROENCEPHALOGRAPHIC FINDINGS IN ACUTE NEPHRITIS. (Journal of Pediatrics, 36: 451, April 1950).

Acute nephritis in children produces changes in brain potentials in the great majority of the patients. It is the opinion of the authors that angiospasm of small cerebral vessels creates ischemia and anoxia which give rise to the electroencephalographic abnormalities. In 24 children with acute nephritis, 164 electroencephalograms were obtained and abnormalities were noted in 22 of the 24 children. The chief changes seen were bursts of slow frequency waves of high microvoltage, instability of the electroencephalographic pattern and suppression of alpha activity associated with an increase of fast frequencies of low amplitude. The character of the electroencephalograms tended to vary from day to day. However, the results show that as acute nephritis persists day after day, there is increased likelihood of electroencephalogram abnormalities, with the brain potentials returning to normal as the nephritis recedes. MICHAEL A. BRESCIA, M.D.

BARR, J. W. AND HARDMANN, W. N.: PAPILLOMA OF THE LARYNX IN A BOY AGE SEVEN. (Canadian Medical Association Journal, 62:376, April 1950).

The authors report the case of a seven-year-old boy with a complaint of hoarseness which had been increasing gradually during the previous two years. At the time of the examination he was unable to talk above a hoarse whisper. There was no weight loss, dyspnea or glandular enlargement. Under general anesthesia a direct laryngoscopy was performed. A warty sessile growth was observed involving the anterior third of the right true vocal cord and the anterior commissure and extending for a short distance subglottically. The tumor was removed by means of an angular laryngeal cup forceps, with very little bleeding. The pathological diagnosis was benign papilloma. Ten days postoperatively the boy was able to talk with a clear tone. A mirror examination of the larynx showed both cords to be intact with normal color and motility. MICHAEL A. BRESCIA, M.D.

Ever doodle like this?

WHEN YOU'RE DAYDREAMING perhaps you, like most people, find yourself doodling pictures of the things you want most.

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Or you're wondering which college you'd like your child to attend a few years from now. Or maybe you'd like to own a *brand-new* automobile someday.

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this Vitamin A and D product

NEVER SAW A FISH

It's ADSORL, a completely synthetic preparation of vitamins A and D in Soriate*, a fat dispersing agent. Because Adsorl is synthetic, it has no fishy odor or taste and does not cause allergic reactions in persons sensitive to fish oils. • When Adsorl is added to solutions such as milk or fruit juices, the Soriate causes the fat soluble vitamins A and D to go into aqueous dispersion, resulting in a homogeneous mixture with uniform distribution of the vitamins. Full dosage is assured, for Adsorl does not settle out or cling to the bottle or glass, as do oily products. • Four drops of Adsorl (0.1 cc.) provide 5000 units of vitamin A and 1000 units of vitamin D. Pharmacies everywhere have Adsorl in 10-cc. and 20-cc. bottles with calibrated dropper.

*T. M. for Emulsifying Ingredients, Abbott.

Abbott